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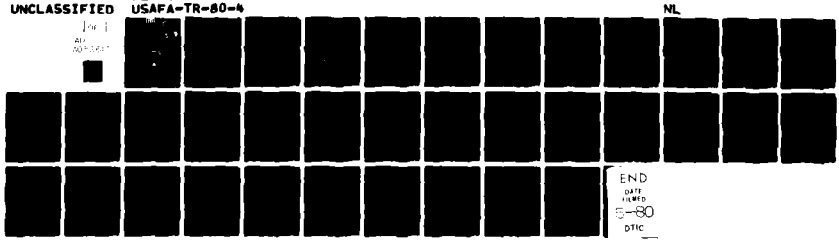

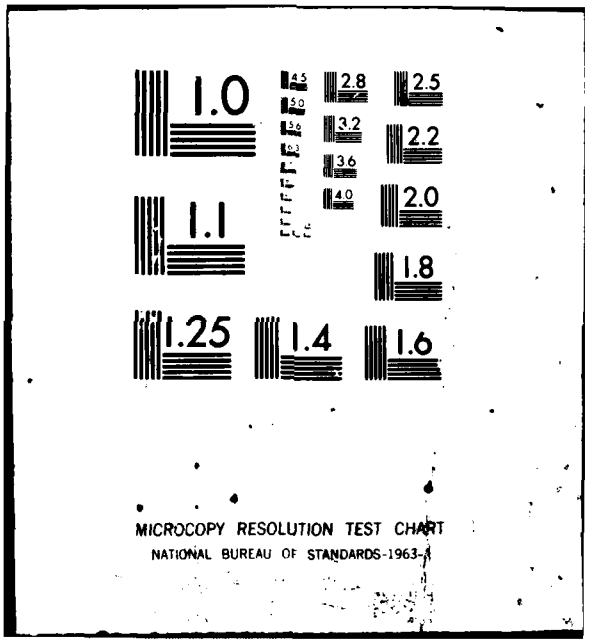
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PROBLEMS ASSOCIATED WITH MEANINGFUL RESEARCH ON THE EFFECTS OF HYPERBARIC OXYGEN ON MYCOTIC DISEASE AGENTS

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FEBRUARY 1980

SUMMARY REPORT

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DEAN OF THE FACULTY
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The effect of hyperbaric oxygen on microorganisms has been investigated over the last 60 years. While work on bacteria has been careful and systematic, work on fungi has been less critical, often yielding conflicting results. An extensive review of the literature was undertaken to define problems associated with meaningful research on the effects of high oxygen pressures on the growth and development of certain human pathogenic fungi. Problem areas defined were significant variability and contradiction of

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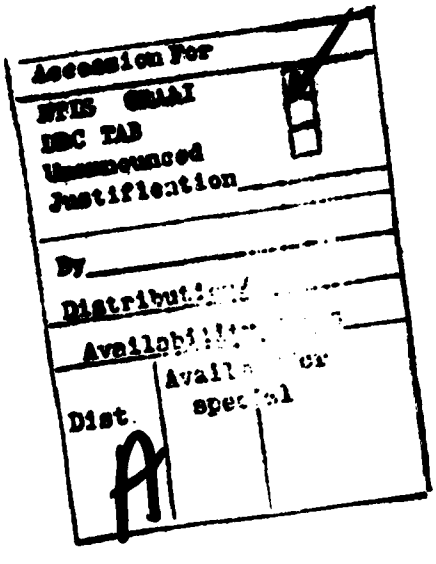
available data; possible erroneous correlations of susceptibility of certain fungi taxa to inhibition by hyperbaric oxygen; questionable reliability of results of past work stemming from possible misidentification of organisms; nomenclatural controversies involving major human pathogenic fungal groups; and questionable reproducibility of certain studies due to the tendencies of certain fungi to change with time and conditions.



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UNITED STATES AIR FORCE ACADEMY

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INTRODUCTION

> "The subject I believe is worthy of investigation by the scientific members of our profession...It is time an effort was made to rescue it...to study its real value; to investigate more completely its effects; and thus place it among the recognized resources of our art."

Extract from a lecture on the "Physiological and Remedial Effects of Increased Pressure of the Atmosphere," Charles A. Lee, Buffalo Medical and Surgical Journal 6: 199-221, 1867, published on the eve of proposed installation of a high pressure chamber at Buffalo (70).

Man adapts admirably to a wide range of conditions imposed upon him by his environment. One of man's tendencies seems to be that of testing his own physiological, psychological, and physical limitations for the sake of profit, pleasure, or other motive. Since prehistory, functioning in the underwater environment has been a particular challenge for man. Assorted devices have been invented to extend man's limitations under water, especially to make it possible for him to breathe (55,56). Devices such as diving bells have been used for many centuries. Aristotle is credited with the design of the first diving bell which was little more than an inverted bucket. Similar devices were used by Alexander the Great during the siege of Tyre. Salvage operations have been a common application of this technology. For example, the Italians used bells for raising galleys from the Lake of Nemi in the 1500's (4).

The first instance where a man actually had compressed air pumped into a brass helmet occurred off Needles, England, in 1754. Since flexibility and mobility were somewhat limited by heavy bells and hoses, Fullerton, an English naval surgeon, suggested as early as 1805 that man should be free to swim and carry with him a reservoir of "condensed air."

The 1800's yielded a number of advances in diving technology. The advent of a safe general use air diving apparatus was responsible for advances in many other aspects of undersea science (19).

One problem of underwater work was the risk of a number of peculiar maladies often referred to as "bends." Divers would surface, and, either immediately or somewhat later, report pain in the joints. This pain could be quite severe. In addition to joint pain, divers would also sometimes cough and report chest pain. Some would experience paralysis or sensory changes. The use of caissons for underwater work on bridges in the later 1800's produced documented cases of the same illnesses (4).

The famous English scientist J.B.S. Haldane, and an associate of his, Captain Damant, recognized the importance of pressure phenomena in undersea and caisson work. In 1905, they produced a series of decompression tables by which divers and caisson workers would ease out of pressure environments by timed increments. These tables eliminated much of the hazard associated with exposure to high pressure. Even before Haldane's tables, it was recognized that since a too sudden release of pressure was responsible for these decompression sicknesses, immediate repressurization would relieve symptoms. Thus, compression chambers were built to repressurize individuals who came to the surface reporting pain. In 1960, the Candadians installed the first compression chamber in North America. Americans had a similar chamber operational by 1891 (19).

With the advent of aviation, man was faced with a new set of physiological limitations. Hypoxia, thermal problems, and spatial disorientation were a few of the difficulties that had to be overcome. The aviation environment was also one of pressure change, however, and as aircraft went

progressively higher, the same decompression sicknesses that had bothered divers for years began to affect aviators. The higher altitudes represented a drop in pressure sufficient to cause serious symptoms.

Most researchers recognized decompression sickness as a condition based upon Henry's Law which explains the evolution of gases from solution with reductions in pressure of the gases above the solution. Compression thereapy was effective in that it was causing evolved bubbles of nitrogen gas to return to solution, thus relieving pressure on tissues caused by the bubbles.

As compression technology progressed, it was discovered that hyperbaric (compression) therapy was effective in treating other medical problems as well. Air emboli could be reduced in size or eliminated in hyperbaric chambers. Gas gangrene could be arrrested as a result of the effect of high oxygen pressures on anaerobic or microaerophilic Clostridium species. Infections caused by certain other bacteria could also be retarded by treatment in compression chambers. Combining high air pressure with the use of 100% oxygen for breathing was particularly effective in inhibiting these organisms (9,16,17,34,43,70).

The United States Air Force initiated a formal hyperbarics program in 1965 for the primary purpose of treating decompression sickness in aircrew members. While this purpose has been realized, the hyperbaric facilities have been used in an increasing number of applications.

Particularly significant have been the effects of compression therapy on certain fungal and fungus-like organisms. The Air Force has successfully treated diseases caused by four different mycotic agents. One of these was a case of pulmonary actinomycosis. The

The effectiveness of hyperbaric oxygen could perhaps have been predicted, considering the low oxygen tolerance of Actinomyces spp.. At least one case of each of systemic coccidioidomycosis, mucormycosis, and aspergillosis has also been treated (4,17). These cases are significant in that Coccidioides immitis, Mucor spp., and Aspergillus spp. involved in such disease processes are not known to be inhibited by oxygen at $PO_2 \simeq 0.21$ atmospheres absolute (abbrev. "ATA"), i.e. oxygen in air at normal sea level pressure. It can be hypothesized that these organisms were somehow inhibited by a partial pressure of oxygen greater than 0.21 ATA but within human oxygen toxicity limits (3 ATA for 90 minutes, empirically).

Some work has been done on the effects of reduced oxygen levels on many fungi (especially soil organisms) (36). No mechanisms are known, however, for the retardation of fungal growth in the presence of elevated pressures of oxygen. Some mechanisms have been hypothesized. Fridovich is a proponent of the possible role of superoxide dismutases in the inhibition of fungi by oxygen (25,26,27). Comparatively little work has been done on the effects of hyperbaric oxygen on fungi.

While the body of literature describing in vitro effects of hyperbaric oxygen on fungi is small, there is essentially no body of literature describing in vivo experiments with fungi and hyperbaric oxygen (34). Part of the reason for this lack of activity may be an unawareness by many competent mycologists and microbiologists of the possible or even theoretical effect of hyperbaric oxygen on fungi. As more in vitro studies are undertaken and data published in widely circulated journals, greater visibility will be given to what could become a very important application of hyperbaric oxygen therapy to medical mycology.

THE SPECIFIC PROBLEMS

In pursuing meaningful studies on the relationship of elevated oxygen tensions to growth and development of human pathogenic fungi, it is imperative that a number of problems be considered. Review of the literature presents the would-be researcher with several dilemmas which include: a) significant variability and contradiction in available data, b) possible erroneous correlations (or non-correlations) of susceptibility of certain fungal taxa to inhibition by increased oxygen levels, c) questionable reliability of results of past work in terms of possible misidentification of organisms used, d) nomenclatural controversies involving major human pathogenic fungal groups, and e) questionable reproducibility of certain studies due to the tendencies of certain human pathogenic fungi to change with time and conditions.

Every living organism has a physiological point at which oxygen is toxic. Organisms classically considered anaerobes may be inhibited by minute amounts of molecular oxygen. This condition has lead to the use of oxygen under pressure to treat patients suffering from gas gangrene, a rapidly progressing necrosis and liquefaction of tissues cased by Clostridium spp., especially Clostridium perfringens (4). Organisms classifically considered aerobes also have points at which oxygen becomes toxic. It has been shown empirically that oxygen levels used to treat gas gangrene can also be effective against Pseudomonas spp. infections secondary to burns and pulmonary mycoses caused by Aspergillus sp., Coccidioides immitis, and members of the Mucorales (4,5).

Some attempts have been made to determine oxygen tolerance levels for a wide range of microorangisms. Gottlieb has compiled a most

excellent summary of such work done through 1971 (34). He lists and discusses all studies carried out on hyperbarics and bacterial, fungal, and viral pathogens, in vivo and in vitro. Gottlieb indicates that studies on fungi have been exploratory and have centered around observations of inhibition of growth in clulture. He states that to his knowledge there were no past or on-going clinical or animal experiments with hyperbaric oxygen on fungal infections. Gottlieb's primary work presently involves the effects of OHP (hperbaric oxygen) on bacteria (35).

One of the earliest papers on OHP and fungi is also one of the most wide ranging. In 1926 Karsner and Saphir reported the influence of high partial pressures of oxygen on the growth of many pathogenic and saprophytic molds (42). They grew these fungi on Sabouraud's medium and exposed them to oxygen levels of 50%-99% for 2.5 to 8 days. Colonial morphology was the criterion for comparison. Human/animal pathogenic organisms used were Microsporon lanosum, Trichophyton fumatum, Tr. gypseum asteroides, Tr crateriforme, Tr. niveium radians, Tr. purpureum, Tr. acuminatum, Tr. gypseum lacticolor, Epidermophyton inquinale, Sporotrichum sp., and Mastigocladium B.. "Plant molds" were reported as Sclerotinia fructicola, Monilia candida, Cryptococcus spp., Allescheria boydii, Aspergillus jeanselmei, Alternaria sp., Dematium chodati, and Oidium suaveolens var. minuta.

The general conclusions of Karsner and Saphir were that oxygen concentrations of 76% or greater had inhibitory effects on most molds in the study and that inhibition tended to be greater in pathogens than in non-pathogens (although pathogenicity could not be correlated exactly with inhibition as some plant pathogens showed no inhibition at all).

Inhibition of growth, when it did occur, was present from the outset, but growth resumed at a normal rate when organisms were removed from the chamber. No organisms were killed by levels of oxygen used. Production of pigments did not seem to be altered in any organism.

In 1938 Williams investigated the differential growth of pathogenic fungi (especially dermatophytes) varying the media and oxygen tensions (74). He grew 18 genera (35 species) of human pathogens on glutamic acid medium and Sabouraud's medium under anaerobic conditions, at 1% O_2, and at 99.5% O_2. He found that under anaerobic conditions no growth occurred for a period of up to 30 days for Achorion schoenleinii, Epidermophyton cruris, E. inguinale, Microsporon audouinii, M. felineum, Trichophyton crateriforme, Tr. granulosum, Tr. gypseum asteroides, Tr. gypseum lacticolor, Tr. niveum, and Tr. sulfureum. Under 1% O_2, these species and others grew on glutamic acid medium but failed to grow on Sabouraud's agar. At 99.5% O_2 organisms were not inhibited but showed a decided tendency to grow subsurface. Williams concluded that the partial pressure of oxygen determined the presence and depth of growth on a given medium and that an organism will invade the medium to seek the optimum atmosphere-medium relationship for growth.

Williams also grew 11 organisms (same as listed above) under increased atmospheric pressures on glutamic acid and Sabouraud's medium. Pressures used were as high as 150 psi (≈10 atm. gauge). Under these conditions no growth was observed on glutamic acid medium. Growth on Sabaurand's medium tended to occur subsurface. Williams' measurement standard was a scale from 5^+ to 0 for both surface and subsurface growth,

matched against seven medium vs. growth level designations. He claims that inhibition of growth at high oxygen tensions should be determined on the basis of some criteria other than his. He suggests growth weight studies.

Some researchers have claimed that Actinomycetes are also inhibited by oxygen. In 1954 Webly claimed that Micromonospora vulgaris was unable to form a surface pellicle in (on) liquid medium when exposed to pure oxygen at one atmosphere pressure. He reports, however, that bottom growth was unaffected or perhaps even stimulated by oxygen (73).

Stuart, et al., 1962, studied the ability of yeast cells to form colonies and retain potassium after exposures ranging from 2 to 143 atmospheres of oxygen. The authors reported their organism as "Bakers' Yeast." Inability to form colonies was seen after a 20-hour exposure to 100 atmosphere (sic) oxygen pressure and much smaller responses at lower pressures. Stuart and coworkers conclude that oxygen tension rather than pressure caused the inhibition because comparable pressures of nitrogen produced no change (68).

Reporting vastly different results were McAllister, et al., 1963, who also worked with yeast cells, specifically Candida albicans (60). McAllister, et al., examined colony growth of a number of bacteria and two aerobic fungi, C. albicans and Aspergillus fumigatus, when exposed to four different oxygen tensions (O_2 to 2 ATA, O_2 at 1 ATA, air at 2 ATA, air at 1 ATA) for 18 hours at 37°C. Both fungi were inhibited at 2 ATA oxygen.

In two papers, Caldwell (1963, 1965) reported tolerance limits of fungi to oxygen somewhere in between limits claimed by Stuart and

McAllister (13,14). Caldwell exposed fungi to 10 atm. oxygen pressure. Aspergillus niger tolerance limit was 18 days, Sordaria fimicola 14 days, and Penicillium cyclopium 10 days. Bacteria exposed to 10 atm. oxygen for up to 14 days were remarkably tolerant and resumed growth immediately after removal of pressure.

Perhaps the most extensive study of the reactions of fungi to increased oxygen levels was carried out by Shiela Robb at the Botany Department, University of Exeter, in 1965 (66). Robb exposed 103 species of fungi to 10 atmospheres oxygen pressure at 25°C for 7 days. 52 resumed growth after treatment. Of these, 22 recovered after 14 days treatment. On resumption of growth, growth patterns were the same as those for untreated organisms after a certain lag period. This lag period varied with species, length of exposure, and, in some cases, replicates of a given species.

The "lag" phenomenon was also noted by Caldwell (14), but not by anyone else (at least not specifically reported). Robb performed a detailed investigation of the lag period on Fusarium solani, Rhizopus arrhizus, Mucor racemosus, and M. plumbeus. Studies showed that lag periods increased with increasing exposure time and that extinction points (points at which all replicates were killed) varied.

In the overall investigation, Robb used 26 Phycomycetes, 16 Ascomycetes, 2 Basidiomycetes, and 59 Fungi Imperfecti. The author claims, "There appears to be no correlation between the taxonomic position of a fungus and its reaction to treatment." This belief is also implicit in conclusions expressed by Karsner and Saphir and by Williams. While the range and diversity of fungi studied by Williams and by Karsner

and Saphir would perhaps not have been wide enough to have allowed them to generalize to any degree in this area, the Robb paper reports on enough organisms to permit observation of trends in inhibition of taxa.

The statement that no correlation exists between taxonomic position and reaction to hyperbaric oxygen is not strictly true. There is enough internal evidence in the Robb paper to indicate that oxygen does tend to inhibit some groups more than others. While no correlation seemed to exist at the class or order level (perhaps due to too small a sample of families or orders upon which to base judgment), some very strong trends were evident at the generic level. Certain genera showed extreme sensitivity for all species tested. Of six species of Helminthosporium tested, all fell into Robb's category of "most sensitive", as did three (all) species of Fusarium, three (all) species of Alternaria, and four (all) species of Phoma. On the other hand, Aspergillus and Penicillium species tested were all very tolerant, very few showing any great sensitivity.

Robb also reports significantly different results with Candida albicans than do McAllister et al. (60). Robb's data indicate Candida albicans to be tolerant to oxygen at 10 ATA for 7^{+} days.

Also from Exeter (1969) is a paper by Gifford and Pritchard which describes the response of Saccharomyces cerevisiae and Candida utilis to hyperbaric oxygen (33). Cultures of both organisms in an exponential growth phase did not undergo any further development when exposed to 10 atm. oxygen. When the exposure was prolonged for several days, all cells died. The carbon source played a role in survivability with cultures surviving longer with ethanol as a carbon source than with

glucose. The authors also reported that exponentially growing populations were more sensitive than stationary phase populations.

In each study to date, the sensitivity of an organism was determined by whether it lived or died, or by reduction in colony size. No work has been done on the developmental cytology of fungal organisms exposed to hyperbaric oxygen.

In evaluating the reliability of the above literature, the known variability of many of the organisms studied and taxonomic controversies surrounding some of the organisms must be considered. Can it be definitely determined, for instance, that Karsner and Saphir actually worked with Trichophyton fumatum, Tr. gypseum asteroides, Tr. crateriforme, and others? Since dermatophyte cultures cannot be kept available for decades (due to in vitro variation with time) it would be difficult to reproduce their work or to base follow-on studies with the same organisms on their data.

Meyer has recognized the problem of variability in dermatophytes and has devised a method of preserving them for up to two years with minimal changes in morphology (61). He states that there are two primary problems in storing dermatophytes: a) They tend to go to a form which produces a white, fluffy, non-sporulating aerial mycelium; and b) some dermatophytes have an evident sensitivity to two narrow temperature ranges, one slightly above zero (0°C) and one slightly below zero. He cites findings of von Kadisch, Lindner, and Luyet (separate studies) in this regard (40,41,57,58). Meyer claims that dermatophytes can be maintained for as long as two years without pleomorphic changes by suspending the fungi in litmus milk or human blood plasma (protective

colloids) and storing at -22°C or -52°C. On the basis of the von Kadisch, Lindner, and Luyet findings, Meyer sees a need to keep the colloid/fungus suspensions at cool room temperature or freeze them hard (<-8.9°C).

Aside from variation of the organisms in culture (two years are considered maximum) taxonomic experts disagree on names and criteria for names of many human pathogenic fungi especially dermatophytes. Leading authorities often disagree between themselves on taxonomic decisions and on descriptions and technical diagnoses which the others have made. In addition, the recent linking of certain dermatophytes with Gymnoascaceae perfect states has not brought unanimous agreement.

It is generally agreed that the soundest basis for dermatophyte taxonomy is a 1934 paper by C. W. Emmons (23). A 1967 work by Ajello (1) reviews the taxonomy of the dermatophytes and related species and updates the 1934 Emmons work. Ajello feels that the three genera Epidermophyton, Microsporum, and Trichophyton are still considered sufficient to accommodate all dermatophytes. He gives descriptions for all species which he considers valid. If one were to have read the Ajello article alone, one would be confident that things were settled, or at least settling, in dermatophyte taxonomy.

That matters are not settled in dermatophyte taxonomy is strongly suggested by a series of papers by George and others on variability in dermatophytes of the very characteristics used to make important taxonomic decisions. In two articles on the relation of nutrition to growth and morphology of Trichophyton violaceum, Georg describes colony formation in this species and the manner in which colonies vary with

nutritional factors and time (28,29). The effect of thiamine on morphology is particularly emphasized.

Hazen has also commented on the advisability of using macroconidial characters for determination of Microsporum species. Hazen claims that the abundance of macrospores can vary from strain to strain of a given species and that nutrition can have a decided effect on morphology and numbers of macrospores produced (38).

In two 1956 papers, Georg discusses concepts in taxonomy and lab identification of Trichophyton tonsurans. In the first paper (30) she presents a critical review of the literature on Trichophyton tonsurans Malmsten 1845 (59). She gives a compilation of more than 35 species names which she feels are all Tr. tonsurans variants. Many of these "species" were used in the Karsner and Saphir research and considered to be separate organisms.

Georg's synonym list is given in table 1. Representative synonymies for three other dermatophytes are given in table 2, 3, and 4. The organisms have been rearranged from the original papers to show taxonomic vs. nomenclatural synonymy.

In the second paper (31), Georg gives a cytological description of the day by day development of what she feels is properly called Trichophyton tonsurans. She describes growth on Sabouraud's dextrose agar which she feels is best for colonial morphology. Her description of Tr. tonsurans is exhaustive and includes excellent line drawings, photomicrographs, and black and white photographs of cultures.

Taschjian and Muskatblitt (69) build on Georg's work in lumping "species" of Trichophyton into Tr. tonsurans. They used hyphal fusion

as a means to indicate that Tr. sabouraudii, Tr. acuminatum, Tr. sulfureum, and Tr. crateriforme are actually all variants of Tr. tonsurans.

Bistis, in a 1959 paper (10), deals specifically with pleomorphism in Trichophyton mentagrophytes (and generally with the remainder of the dermatophytes). He is dissatisfied with the classification of dermatophytes (especially Trichophyton) on the basis of conidium production because of the extreme sensitivity of this character to environmental change. Rippon and Scherr (65) go beyond Bistis and present evidence for dimorphism in dermatophytes. They subjected Trichophyton rubrum, Microsporum audouinii, and Cladosporium mansoni to increasing levels of cysteine. As cysteine increased all organisms tended to go to a yeast form and demonstrated a greater ability to invade deep tissue.

The relationship between certain conidial state organisms of medical importance and ascogenous perfect states has been recognized for decades. Penicillium and Aspergillus are linked with certain Eurotiaceae perfect states (8,21,24). Dermatophytes are usually linked with perfect states in the Gymnoascaceae (2,12,18,22,52,67). As there is controversy over naming of imperfect state dermatophytes, there is equal to greater controversy over the identification of the perfect states of these organisms.

Kuehn and Orr have published a series of papers on the family Gymnoascaceae and have identified and described numerous genera of the Gymnoasaceae (44,45,46,47,48,49,50,51,52,53,64). Orr has repeatedly urged caution in identification of human pathogens. In one paper, for instance, Orr describes his isolation of 64 fungal species from soil in which Coccidioides immitis was known to be endemic. In addition to the consistent recovery of C. immitis from these samples, it was noted that

many of the fungi produced asexual spores similar to those of C. immitis and could easily have been confused with C. immitis in superficial identification work (63). Emmons reflects the same caution as Orr. In isolating Myxotrichum and Gymnoascus from the lungs of animals, he reports that 9 strains of Myxotrichum and 3 strains of Gymnoascus attracted attention because of their strong microscopic resemblance to Coccidioides (22).

Orr and Kuehn in a 1971 review of Gymnoascaceae organisms rigidly critiqued some recent taxonomic work performed on the Gymnoascaceae and noted a number of inaccuracies and questionable identifications of new species (64). In support of their position, the authors obtained cultures of some supposed new species and found that these cultures did not have many of the characteristics described or inferred by those who had described them. Orr and Kuehn single out as inaccurate the identification of Thailandia candida nov. gen. et nov. sp. described by Vardhanabhuti as a new human pathogen (72). Orr says that Lodder has identified Vardhanabhuti's organism as Candida tropicalis (Cast.) Berhout.. Vardhanabhuti claimed that his new species produced a sexual stage when injected intraperitoneally into laboratory animals, and described "spherules" and "endospores."

Orr and Kuehn also take exception with Apinis' placement of what they conclude to be Penicillia into the family Gymnoascaceae (3). Orr places the disputed genera in the family Eurotiaceae. Apinis has also redescribed some of the organisms initially described by Orr (51). Orr feels that Apinis' taxonomic decisions are open to question.

Orr and Kuehn refute the diagnosis of Narasimhella, a new genus

described by Thirumalacher (71) and placed by him in the Gymnoascaceae. Orr identifies Narasimhella poonensis as Pseudoarachniotus marginosporus, a species described by himself and Kuehn.

Hughes has attempted to compile Gymnoascaceae taxonomic data through 1968 (39). Orr disagrees with the taxonomic significance of Hughes' work, feeling that Hughes overlooked a number of highly important criteria (64).

There is also controversy in the literature over the tendency of various workers to lump dermatophyte perfect states into the Gymnoascaceae. Bose is particularly concerned over the appropriateness of the term "Gymnoascaceae" for the dermatophyte sexual stages. Bose urges caution in lumping all dermatophyte perfect states under Gymnoascaceae and Gymnoascus. Some are described as having perithecia and cleistothecia which Bose feels is inconsistent with the Gymno- designation (11). Stockdale reflects this same opinion in the paper in which Nannizzia incurvata is described as a perfect state of Microsporum gypseum (67). Both Stockdale and Bose also feel that Microsporum gypseum is probably the imperfect state of several genera of the Gymnoascaceae.

Earlier disagreements on taxonomic work also surround the appropriateness of "Gymnoascaceae." Griffin (37) reports Nannizzi as having described in 1927 the production of cleistothecia by Microsporum gypseum (Bodin) Guiart & Grigorakis, naming it Gymnoascus gypseum Nannizzi. Nannizzi was severly criticized by Langeron and Milochevitch in 1930 for impure cultures and poor technique. Nannizzi's work was considered incorrect (or at least open to question) until Griffin in 1960

rediscovered what Nannizzi had described in 1927. Griffin also discusses "abortive cleistothecia" produced by Trichophyton terrestre Durie & Frey. He says that although no asci have been found in these "cleistothecia-like" structures, that, should they be found, Tr. terrestre would probably be found to be a member of Gymnoascaceae.

In a critical survey of the production of perfect states in dermatophytes described through 1960, Benedek questions the validity of placing any of the dermatophytes in association with the Gymnoascaceae. He feels that evidence is far too sketchy and that much work of this nature represents unwarranted generalization (6).

It is evident in surveying the literature that most work on Gymnoascaceae has either been taxonomic or cytological-morphological and that little work has been done on the physiology of the group. Ghosh has made a starting contribution in comparing the physiology of a number of species of Gymnoascaceae. She reports results of studies on nitrogen assimilation, carbon assimilation, vitamin requirements, and trace element requirements. No great taxonomic conclusions are drawn (32). Kuehn has also worked out the nutritional requirements of Arthroderma tuberculatum in an attempt to find a medium which would sustain A. tuberculatum through repeated cultures and maintain good dependable characteristics (48).

It is interesting to note that Kuehn, Orr, and others familiar with (and convinced of) the link between imperfect state human pathogens and the Gymnoascaceae will almost always refer to the organisms by their perfect state (i.e. Ascomycete) names, whereas most medical mycology references are content to perpetuate the names of the imperfect states. Quality medical mycology manuals (7,15,23,54,62) seem to be authored by

individuals quite cognizant of synonymy and nomenclatural problems who desire to stay out of the controversies.

Finally, it is noteworthy that no article describing reactions of fungi to hyperbaric oxygen addresses the question of dermatophyte perfect states. Furthermore, no author even makes an attempt to link oxygen sensitivity to the taxonomic position of a fungus on the basis of the perfect state. Since there does seem to be some sensitivity to oxygen at the generic level as Robb's study would indicate, perhaps studies of such sensitivity would be helful in elucidating relationships between various dermatophytic fungi and would create an additional parameter for linking perfect and imperfect states.

Further work in the area of hyperbarics and mycotic disease agents should be encouraged. Preliminary research shows promise that significant benefit might accrue to this area of medical mycology. Would-be researchers should be aware of these problem areas, however, in order to avoid a number of possible pitfalls.

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Table 1.

Georg has compiled the following list of synonyms for Trichophyton tonsurans (30). (Cairney responsible for this arrangement of synonyms.)

Trichophyton tonsurans

≡ Oidium tonsurans

= Trichophyton sabouraudi

= Trichophyton crateriforme

≡ Chlamydoaleurosporia crateriformis

≡ Endothrix crateriforme

= Trichophyton acuminatum

≡ Aleurosporia acuminata

≡ Endothrix acuminatum

= Trichophyton regulare

= Trichophyton fumatum

= Trichophyton exsiccatum

= Trichophyton polygonum

= Trichophyton cerebriforme

= Trichophyton circonvolutum

= Trichophyton effractum

≡ Aleurosporia effracta

= Trichophyton umbilculatum

= Trichophyton pilosum

= Trichophyton plicatile

≡ Neotrichophyton plicatile

≡ Aleurospora plicatilis

Table 1. (cont.)

= Trichophyton sulfureum

≡ Endothrix sulfureum

= Trichophyton flavum

≡ Neotrichophyton flavum

= Trichophyton ochropyrraceum

= Trichophyton rotundum

= Trichophyton bicolor

= Trichophyton cineraceum

= Trichophyton acutulum

= Trichophyton areolatum

= Trichophyton germen I.

= Trichophyton floriforme

≡ Favotrichophyton floriforme

= Trichophyton fuscum

Table 2.

Beneke and Rogers (7) have compiled the following list of synonyms for Trichophyton mentagrophytes. (Cairney responsible for arrangement of synonyms.)

Trichophyton mentagrophytes

≡ Microsporon mentagrophytes

≡ Ectotrichophyton mentagrophytes

= Achorion quinkeanum

= Trichophyton felineum

= Trichophyton gypseum

= Trichophyton equinum

= Trichophyton granulosum

= Trichophyton radiolatum

= Trichophyton lacticolor

= Trichophyton niveum

= Trichophyton radians

= Trichophyton denticulatum

= Trichophyton persicolor

= Trichophyton farinulentum

= Trichophyton asteroides

= Trichophyton interdigitale

= Trichophyton pedis

Table 3.

Beneke and Rogers (7) have compiled the following list of synonyms for Microsporum gypseum. (Cairney responsible for arrangement of synonyms.)

Microsporum gypseum

≡ Achorion gypseum

= Microsporum flavum

= Microsporum flavescens

= Microsporum scortium

= Microsporum xanthodes

Table 4.

Beneke and Rogers (7) have compiled the following list of synonyms for *Microsporum canis*. (Cairney responsible for arrangement of synonyms.)

Microsporum canis

= *Microsporum felineum*

= *Microsporum equinum*

= *Microsporum lanosum*

≡ *Sabouraudites lanosus*

= *Microsporum caninum*

= *Microsporum stilliansi*

= *Microsporum auriatiacum*

= *Microsporum pseudolanosum*

= *Microsporum simiae*

= *Microsporum obesum*

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